STRUCTURAL BIOLOGY OF MEMBRANE PROTEINS

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PARTICIPATING INSTITUTES AND CENTERS (ICs):

National Institute of General Medical Sciences
National Cancer Institute
National Institute on Aging
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Deafness and Communicative Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Environmental Health Sciences
National Institute of Mental Health
National Institute of Neurological Disorders and Stroke

THIS PA CONTAINS THE FOLLOWING INFORMATION

o Purpose of the PA
o Research Objectives
o Mechanism(s) of Support
o Eligible Institutions
o Individuals Eligible to Become Principal Investigators
o Where to Send Inquiries
o Submitting an Application
o Peer Review Process
o Review Criteria
o Award Criteria
o Required Federal Citations

PURPOSE OF THIS PA

The purpose of this program announcement (PA) is to encourage basic research on the structures of membrane proteins at atomic resolution. It replaces and updates previous program announcements (PA-99-004 and PA-95-035), which were issued under the same title.

Considerable research is ongoing in the area of membrane protein structure and function, yet relatively few investigators have applied the techniques of x-ray crystallography, electron diffraction, or nuclear magnetic resonance (NMR) spectroscopy to study directly the structures of their proteins. During the past decade, approximately 30 membrane protein structures have been solved and each structure has been a major contribution in its area of science (see: http://blanco.biomol.uci.edu/Membrane_Proteins_xtal.html). This progress clearly demonstrates that obtaining membrane protein structures is feasible. However, during this same decade the rate of soluble protein structure solution has accelerated greatly and there remains a gap between the understanding of membrane proteins and their soluble protein counterparts.

The Protein Structure Initiative (PSI) (see: http://www.nigms.nih.gov/funding/psi.html) proposes to accelerate the rate of protein structure solution even more. Some of the PSI centers include efforts to determine membrane protein structures, and the PSI program announcements encourage support of technology development for high-throughput approaches to membrane protein structure determination (see: http://grants.nih.gov/grants/guide/pa-files/PA-99-116.html). Nonetheless, there remains a need for a separate program initiative that focuses primarily on membrane proteins and the development of methods for solving their structures. An increase in the number of known membrane protein structures will contribute to an enhanced understanding of many basic phenomena underlying cellular functions essential to human health.

RESEARCH OBJECTIVES

Membrane proteins play a crucial role in many cellular and physiological processes. They are essential mediators of material and information transfer between cells and their environment, between compartments within cells, and between compartments comprising the organ systems. Functionally normal membrane proteins are vital to health and specific defects are associated with many known disease states. Membrane proteins are the targets of a large number of pharmacologically and toxicologically active substances and are responsible, in part, for their uptake, metabolism, and clearance.

Despite the importance of membrane proteins, the knowledge of their high resolution structures and mechanisms of action has lagged far behind the knowledge of these properties of proteins in general. This has resulted from the difficulty of obtaining x-ray diffraction-quality crystals for the

membrane proteins and the difficulty of applying well-developed solution NMR methods to the study of most membrane proteins. These difficulties have led to a reluctance of many investigators to pursue high resolution structural studies of membrane proteins. However, in the recent past, advances in methods for crystallization and analysis of proteins by x-ray and electron diffraction methods, and improvements in NMR methods, have led to new opportunities. Further, the solution of crystal structures, once suitable crystals are obtained, has, in many cases, become sufficiently routine, that crystallization itself is often the more challenging undertaking. For this program announcement, therefore, protein production, protein crystallization, and structure solution are all considered worthy aims.

The objective of this program announcement is two-fold:

1) To encourage more investigators with interests in membrane associated systems to pursue high resolution structural studies making use of these recently developed technologies; and

2) To encourage additional research to further develop methods for studying the structure of membrane proteins at atomic resolution.

Examples of methods identified as needing specific attention include, but are not limited to:

o Methods for over-expression of native and modified membrane proteins;

o Methods for isolation, purification, and stabilization of membrane proteins, including the development of new detergents and non-detergent solubilization agents;

o Methods for crystallization of membrane proteins and crystal manipulation that could facilitate data collection;

o Methods for electron diffraction, particularly for the production of suitable 2D-crystals;

o Methods for NMR analysis of membrane proteins in solution, in micelles, and in their native lipid environments;

o Methods to elucidate the organization of lipid and detergent molecules within protein crystalline arrays (e.g., neutron diffraction).

The techniques of x-ray or electron diffraction and of NMR spectroscopy have been emphasized in this announcement, since they presently show the most promise for producing the most complete high resolution information for the largest number of proteins. However, other methods that can provide atomic resolution information in selected cases are also of interest.

It is expected that many of the projects will be collaborative efforts between biochemists and molecular biologists with expertise in the isolation and characterization of membrane-bound proteins and biophysicists with expertise in x-ray crystallography, NMR, and other structural methods. A major aim of this program announcement is to stimulate such collaborations.

The following are examples of the types of membrane proteins of interest to the participating institutes:

o Membrane protein systems of particular interest to the National Institute of General Medical Sciences (NIGMS) include: energy transducing membranes of mitochondria, chloroplasts, and bacterial cell membranes involved in electron transport and ATP synthesis; channels, pores, and transporters of ions, substrates, and macromolecules between intracellular compartments and between the cell and its environment; enzymes in the synthesis and metabolism of lipids, membrane-associated and secreted proteins, and glycoconjugates; cytoskeletal proteins, including those required for intracellular vesicle transport, cell motility, and cell division; regulators of cell-cell communication, differentiation, and growth; receptors relevant to cell cycle regulation, mechanisms of anesthetic action, and trauma and burn physiology; transporters and enzymes responsible for the uptake, metabolism, and clearance of drugs, or in other ways affecting the bioavailability, pharmacokinetics, or action of drugs; targets of drug action and toxicity, including targets of naturally occurring toxins and venoms; and enzymes involved in the biosynthesis of natural products.

o Membrane proteins and membrane complexes of interest to the National Cancer Institute include those associated with the biology, diagnosis and treatment of cancer. Proteins of specific interest include those membrane proteins whose alterations have been shown to be linked to the development and progression of cancer. In addition membrane proteins that are part of cancer related signaling pathways are also of interest. Of special interest are the proteins associated with the extracellular matrix (for example laminins and fibronectin). Proteins with potential as diagnostic markers and/or therapeutic targets will also be of high interest. The National Cancer Institute is also soliciting applications focused on the development of new approaches and technologies for the isolation, purification, and structure determination of these proteins.

Applicants strictly focused on technology should consider applying under the NCI Innovative Molecular Applications of Technology Program. See: http://otir.nci.nih.gov/tech/funding.html.

o Membrane protein systems of interest to the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) have specific relevance to one of the following programmatic areas: muscle function and disease; bone and cartilage function and disease; and skin function and disease. Examples of NIAMS interests are: structural aspects of membrane proteins in muscle disease, excitation, relaxation, force transduction, cellular homeostasis and metabolism, regulators of cell-cell communication and attachment (e.g., costameres, myotendinous and neuromuscular junctions), ion channels, receptors, transporters and enzymes that effect muscle function and hypertrophy or atrophy; and structural aspects of membrane proteins in skin as they are involved in the establishment of the stratum corneum barrier, epidermal cell-cell attachment and communication, transmembrane signaling and transport, and cell movement, including genetic and acquired diseases of skin in which the membrane protein is defective or targeted (which may encompass both benign and malignant hyperproliferative diseases).

o Membrane protein systems of interest to the National Institute on Deafness and Communication Disorders (NIDCD) include proteins involved in the auditory, vestibular, olfaction, smell, voice, speech and language sensory systems. Of special interest are eukaryotic protein systems including transport proteins, ion channels, ligand receptors, G-protein coupled receptors, transcription and associated factors, motor and motor associated proteins, growth factor receptors, and cytoskeletal structural components involved in the function of these sensory and neural functions. Further, the NIDCD is also interested in prokaryotic membrane proteins from numerous viral and microbial organisms involved in otitis media. In addition to multiple eukaryotic host cell receptor ligands, these prokaryotic proteins would include microbial specific factors such as muscin, and other potential proteins serving as identifiable markers for middle ear infections.

o Membrane protein systems of particular interest to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) should have specific relevance to one of the following programmatic areas: diseases of transport such as cystic fibrosis and peroxisomal biogenesis disorders; carbohydrate metabolism and its hormonal control; diabetes mellitus; hormone receptors and signal transduction; endocrine disorders; normal and abnormal processes of lipid, protein, amino acid, urea, pyrimidine, metal ion and steroid metabolism; and genetic metabolic disorders. Proteins should be of mammalian origin. Studies on proteins of prokaryotic or lower eukaryotic origin should be proposed as models for mammalian systems. An example of this is the ATP Binding Cassette transporter superfamily or traffic ATPases in bacteria and

yeast that serve as models for the cystic fibrosis transmembrane regulator (CFTR).

o Membrane protein systems of particular interest to the National Institute of Environmental Health Sciences (NIEHS) include those proteins/enzymes involved in the response of cells to environmental toxicants. These proteins/enzymes may include the components of the stress signaling pathway, ion channels involved in transport of xenobiotics (e.g., membrane transporters as PgP and MDR, MRP2, transporters and enzymes responsible for the uptake metabolism and clearance of environmental toxicants, targets of toxicant action including the Ah receptor nonclassical receptors for endocrine disrupting agents, and membrane bound heat shock proteins).

o Membrane protein systems of interest to the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Mental Health (NIMH), and the National Institute on Aging (NIA) include neurotransmitter and growth factor receptors, transporters, ion pumps, voltage- and ligand-gated ion channels, trafficking proteins, mitochondrial proteins, structural proteins and other proteins involved in the normal function and pathology of cells (neurons and glia) in the central and peripheral nervous system. An additional interest is in proteins involved in synaptic transmission and in the regulation, metabolism, and homeostasis and signaling in the brain during functions such as learning and memory or cognition, during development and aging into late-life, and in CNS disorders.

Summary

The purpose of this program announcement is to stimulate research leading to the solution of membrane protein structures at atomic resolution. The above listings are not meant to be exclusive. Structural information obtained for any membrane protein will contribute to understanding the general principles that underlie all membrane protein structure and function. Research on the non-membrane proteins associated with many of the cellular functions listed above is also supported by the participating Institutes. However, this program announcement is intended to emphasize the need for additional research on structural aspects of the membrane proteins involved in these processes.

MECHANISM(S) OF SUPPORT

This PA will use the NIH R01 award mechanism(s). As an applicant, you will be solely responsible for planning, directing, and executing the proposed project.

Some research efforts may be more appropriate for the Program Project (P01) grant mechanism or the Integrative and Collaborative Approaches to Research (R24) grant mechanism. Investigators interested in applying for P01 or R24 grants should contact the program staff listed under inquiries to ascertain which Institutes may allow such applications.

A program announcement on the Structural Biology of Membrane Proteins for Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) applications also has been issued (see: Insert URL when published).

This PA uses just-in-time concepts. It also uses the modular as well as the non-modular budgeting formats (see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, if you are submitting an application with direct costs in each year of $250,000 or less, use the modular format. Otherwise follow the instructions for non-modular research grant applications.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

o For-profit or non-profit organizations
o Public or private institutions, such as universities, colleges, hospitals, and laboratories
o Units of State and local governments
o Eligible agencies of the Federal government
o Domestic or foreign

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups, as well as individuals with disabilities, are always encouraged to apply for NIH programs.

WHERE TO SEND INQUIRIES

We encourage your inquiries concerning this PA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

o Direct your questions about scientific/research issues to:

Peter C. Preusch, Ph.D.
Division of Pharmacology, Physiology, and Biological Chemistry
National Institute of General Medical Sciences
45 Center Drive, MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-5938
FAX: (301) 480-2802
Email: preuschp@nigms.nih.gov

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National Institute of General Medical Sciences
45 Center Drive, MSC 6200
Bethesda, MD 20892-6200
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Randall R. Stewart, Ph.D.
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National Institute of Neurological Disorders and Stroke
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Telephone: (301) 496-1917
FAX: (301) 402-1501
Email: stewartr@ninds.nih.gov

o Direct your questions about peer review issues to:

Donald Schneider, Ph.D.

Division of Molecular and Cellular Mechanisms
Center for Scientific Review
Rockledge 2/RM 4172, MSC 7806
Bethesda, MD 20892-7806
Telephone: (301) 435-1727
FAX: (301) 480-2327
Email: schneidd@drg.nih.gov

o Direct your questions about financial or grants management matters to:

Ms. Grace Tuanmu
Grants Administration Branch
National Institute of General Medical Sciences
45 Center Drive, MSC 6200
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FAX: (301) 480-2554
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Mr. William Wells
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FAX: (301) 402-0219
Email: tc48k@nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

APPLICATION RECEIPT DATES: Applications submitted in response to this program announcement will be accepted at the standard application deadlines, which are available at http://grants.nih.gov/grants/dates.htm. Application deadlines are also indicated in the PHS 398 application kit.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS: Applications requesting up to $250,000 per year in direct costs must be submitted in a modular grant format. The modular grant format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in $25,000 modules. Section C of the research grant application instructions for the PHS 398 (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.html includes step-by-step guidance for

preparing modular grants. Additional information on modular grants is available at http://grants.nih.gov/grants/funding/modular/modular.htm.

SPECIFIC INSTRUCTIONS FOR APPLICATIONS REQUESTING $500,000 OR MORE PER YEAR:
Applications requesting $500,000 or more in direct costs for any year must include a cover letter identifying the NIH staff member within one of NIH institutes or centers who has agreed to accept assignment of the application.

Applicants requesting more than $500,000 must carry out the following steps:

1) Contact the IC program staff at least 6 weeks before submitting the application, i.e., as you are developing plans for the study;

2) Obtain agreement from the IC staff that the IC will accept your application for consideration for award; and,

3) Identify, in a cover letter sent with the application, the staff member and IC who agreed to accept assignment of the application.

This policy applies to all investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended or revised version of these grant application types. Additional information on this policy is available in the NIH Guide for Grants and Contracts, October 19, 2001 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the checklist, and five signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

APPLICATION PROCESSING: Applications must be received by or mailed before the receipt dates described at

http://grants.nih.gov/grants/funding/submissionschedule.htm. The CSR will not accept any application in response to this PA that is essentially the same as one currently pending initial review unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of a substantial revision of an application already reviewed, but such application must include an Introduction addressing the previous critique.

PEER REVIEW PROCESS

Applications submitted for this PA will be assigned on the basis of established PHS referral guidelines. An appropriate scientific review group convened in accordance with the standard NIH peer review procedures (http://www.csr.nih.gov/refrev.htm) will evaluate applications for scientific and technical merit.

As part of the initial merit review, all applications will:

o Receive a written critique
o Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score
o Receive a second level review by the appropriate national advisory council or board

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of your application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals:

o Significance
o Approach
o Innovation
o Investigator
o Environment

The scientific review group will address and consider each of these criteria in assigning your application's overall score, weighting them as appropriate for each application. Your application

does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, you may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) SIGNIFICANCE: Does your study address an important problem? If the aims of your application are achieved, how do they advance scientific knowledge? What will be the effect of these studies on the concepts or methods that drive this field?

(2) APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Do you acknowledge potential problem areas and consider alternative tactics?

(3) INNOVATION: Does your project employ novel concepts, approaches or methods? Are the aims original and innovative? Does your project challenge existing paradigms or develop new methodologies or technologies?

(4) INVESTIGATOR: Are you appropriately trained and well suited to carry out this work? Is the work proposed appropriate to your experience level as the principal investigator and to that of other researchers (if any)?

(5) ENVIRONMENT: Does the scientific environment in which your work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, your application will also be reviewed with respect to the following:

PROTECTIONS: The adequacy of the proposed protection for humans, animals, or the environment, to the extent they may be adversely affected by the project proposed in the application.

INCLUSION: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria included in the section on Federal Citations, below.)

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

OTHER REVIEW CRITERIA: A premise of this program announcement is that protein production and crystallization, not just structure solution, are worthy aims requiring support. Therefore, lack of crystals that diffract to high resolution should not be considered a weakness of a proposal. The availability of such crystals may be considered a strength.

AWARD CRITERIA

Applications submitted in response to a PA will compete for available funds with all other recommended applications. The following will be considered in making funding decisions:

o Scientific merit of the proposed project as determined by peer review
o Availability of funds
o Relevance to program priorities

REQUIRED FEDERAL CITATIONS

It is not anticipated that proposals submitted in response to this PA will involve human subject studies.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at
http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include

information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

Applicants are reminded of the NIH policy that requires the deposition of atomic coordinates of solved protein structures into structural databases. See: http://grants.nih.gov/grants/guide/notice-files/not99-010.html.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance No. 93.113, 93.173, 93.242, 93.396, 93.821, 93.846, 93.847, 93.854, 93.859, and 93.866, and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284)and administered under NIH grants policies described at http://grants.nih.gov/grants/policy/policy.htm and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Return to Volume Index

Return to NIH Guide Main Index